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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

September 15, 1999

Re: Docket No. 980-0077, CDER 98 182: Draft Guidance for Industry; Clinical Development Programs for Drugs, Devices, and Biological Products Intended for the Treatment of Osteoarthritis (OA)

Dear Sir/Madam:

Reference is made to FDA's issuance of draft Guidance. for Industry; Clinical Development Programs for Drugs, Devices, and Biological Products Intended for the Treatment of Osteoarthritis (OA) (*Federal Register* Vol 64: Doc. 99-18031, July 15, 1999). This notice requested that written comments or suggestions be submitted to FDA within 60 days of publication. The purpose of this letter is to provide comments on this draft guidance document.

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, neurological disorders, and joint replacements.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1998, pharmaceutical research and development spendmg totaled $1.4 billion. For these reasons, we are very interested in commenting on this proposed Guidance.

Bristol-Myers Squibb is supportive of the FDA initiative to draft clinical- guidance for development of products for treatment of osteoarthritis (Ok). We have reviewed the draft guidance. Our comments and suggestions are listed below, with reference to the section numbers of the draft guidance.

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II. Use of Preclinical Models

- We recommend that the guidance be revised to encourage inclusion of any data with potential biomarkers or surrogate endpoints(ie. imaging techniques; tissue biopsies; serum, joint or urine fluid constituents) obtained from OA animal models, especially if similar markers or endpoints will be investigated in clinical trials.

- The guidance correctly identifies the utility of incorporating toxicity endpoints into studies of pharmacodynamic models as a screen for potential toxicity associated with the product. However, the recommendation for parallel assessment of therapeutic activity and toxicity appears impractical given the differences in' study endpoints and the range of doses investigated. We also note that toxicology models are typically selected because of the broad historical' background data available on the species and/or strain being used and rarely would be the same as nharmacodvnamic models-used to evaluate OA products. We recommend that the reference to "parallel assessments of activity and toxicity" be deleted from the guidance.

IV. Osteoarthritis Measurements; Structure

- Radiographic (x-ray) evaluation remains a limited tool to measure structural changes in the joint, due to difficulties both in standardizing patient position and interpreting OA progression based on an image from a single plane, Therefore, the measurement of joint-space-narrowing (JSN) via x-rays provides only limited value and may not reflect the complicated biological processes involved in the progression of osteoarthritis. We recommend that the guidance be expanded to encourage the development and the use of better tools that reflect all elements of the joint involved-in the anatomical deterioration. The guidance should note the utility of emerging MRI technology and its promise in measuring structural change in joints.

V. Osteoarthritis claims

- The guidance regarding the approvability of a claim for "delay in structural progression" should be clarified with respect to the concurrent data required demonstrating effectiveness on "signs and symptoms". We also recommend revision of the second paragraph under section V.B. and incorporation of this text into the introduction to section V.

- The guidance on data to support delay in structural progression is specific to data demonstrating effectiveness in joint-space-narrowing (JNS). No other techniques appear acceptable beside planar x-ray in the draft document. As noted above, we recommend that this portion of the guidance be generalized to include data from other imaging techniques demonstrating prevention of structural damage/arrest of structural damage/repair of structural damage, based on adequate comparative imaging techniques. Emerging MRI technologies offer well defined imaging including spatial vision of joint elements, and may reduce sample size requirements versus those required in studies using x-ray evaluation of JSN. Structural efficacy demonstrated for a minimum period (ie. 1 year) on the basis of an MRI surrogate can be further validated in Phase IV trials.

- The requirement for a minimum reduction of 50% in structural progression vs. control is extreme,, We recommend that the guidance specify a smaller reduction (eg. 30%) if shown to be clinically meaningful as determined by adequate and well-controlled clinical investigation.

- The-draft guidance suggests that a claim for the "prevention of the occurrence of OA" using symptomatic and radiographic criteria in new joints in patients with OA or in individuals at risk to develop OA is possible. We agree there- will likely be challenges in resolving assessment issues for designs capable of properly validating this claim, and in defining the term "new OA." Despite these challenges, BMS is in favor of further discussions between FDA, industry, and academic investigators to address these issues and to develop more definitive guidelines surrounding this claim.

VI. Trial Designs and Analyses

- The draft guidance correctly identifies the need to adjust the p-value used for the primary and secondary analyses when-multiplicity is present. This may be due to multiple primary variables/endpoints, multiple comparisons of treatments, repeated evaluation over time, and/or interim analyses. In trials with multiple primary endpoints, the ICH-E9 guidelines note that the extent of intercorrelation among the proposed primary variables should be considered in evaluating the impact of Type-I error, Therefore, if the purpose of the trial is to demonstrate effects on all primary variables, there is no need for adjustment of the Type-I error.

Regardless of whether there is a single primary endpoint or multiple primary endpoints, with or without adjustment for a Type-I error, it would not be necessary to adjust for one or more secondary variables/endpoints as the secondary variables are only either supportive measurements related to the primary objective or measurements of effects related to secondary objectives. Secondary variables may be individually tested for significance without adjustment, so long as the primary variable(s) is (are) shown to be significant.
Reference: International Conference on Harmonisation; Guidance on Statistical Principles for Clinical Trials; Availability. *Department of Health and Human Services; FDA.* Docket No. 97D-0174, Federal Register Vol. 63, No. 179, 1998.

- The draft guidance identifies the possibility of a "categorical rating (akin to ACR20 in RA)" for OA as a means of determining product effectiveness. We agree such a categorical rating should be useful. We are aware that FDA/NIH-sponsored joint government/academia/ industry initiative is underway to identify and possibly validate such a rating for OA. We recommend that the guidance be changed to note current efforts in this regard and to encourage the use of validated rating methods.

- As noted in comments above, MRI imaging techniques hold the promise of identifying the effect of a product on the complete signal joint. We recommend that FDA assemble a joint government/ academia/industry panel including statisticians to identify a credible index of joint structure to be used to measure and analyze structural change.

VII. Assembling the Evidence

- If the recommendation of the Arthritis Advisory Committee is, accepted and the guidance is changed to identify separate OA claims in hip/knee, hand, and spine, the test in this section should clarify the evidence required to support subsequent claims in other signal joints. We recommend that these claims be approved on the basrs of a single trial, as the product's mechanism of action was validated in the adequate and well-controlled clinical study(ies) supporting the initial claim.

Bristol-Myers Squibb appreciates the opportunity to comment on this draft guidance and would be pleased to work with FDA in addressing the very important issues presented in the draft guidance.

Sincerely,

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